REMARKS/ARGUMENTS

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-123 are pending in this application and are rejected on various grounds. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 U.S.C. §§101 and 112, First Paragraph

Claims 119-123 remain rejected under 35 U.S.C. §101 for lack of utility. Claims 119-123 are further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention." For the reasons outlined below, Applicants respectfully disagree.

The Examiner says that "(t)he instant application does not disclose the biological role of this protein or its significance..."

Applicants respectfully submit that utility for PRO830 polypeptides is based on the 2.188 fold to 2.549 -fold gene amplification observed for the DNA encoding PRO830 in lung tumors and that the data presented in Example 170 starting on page 539 of the specification and the cumulative evidence of record, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention. As evidence that the "increase in DNA" in the gene amplification assay is significant, Applicants submit a Declaration by Dr. Audrey Goddard. This Declaration provides a statement by an expert in the relevant art stating that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the 2.188 fold to 2.549 -fold in lung primary tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

The Examiner contends on page 5 of the instant Final Office Action dated June 13, 2005 that "the specification provides data showing a very small increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO830."

Applicants submit that, as any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even with most tumors. Whether the PRO830 gene is amplified in few tumor samples or in the vast majority of tumor samples studied is not relevant to its identification as a tumor marker, or its patentable utility. Rather, whether the amplification data for PRO830 is considered significant is what lends support to its usefulness as a tumor marker. Thus, while a positive result does indicate the presence of cancer, a negative result requires further follow up testing, testing which is considered routine by one skilled in the art of oncology and is not considered undue. Again, as evidence that the "increase in DNA" in the gene amplification assay is significant, the Declaration by Dr. Audrey Goddard enclosed herewith provides a statement by an expert in the relevant art stating that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay. Therefore, Applicants submit that the Examiner seems to be applying a heightened utility standard in this instance, which is legally incorrect.

The Examiner further cites references Doerks *et al.*, Brenner *et al.*, Bork *et al.* to show that "sequence-to-function methods of assigning protein function are prone to errors..." Applicants submit that their assertion for utility of PRO830 is not based on structural similarity. Instead, as indicated above, utility for PRO830 polypeptides is based on the gene amplification observed for the DNA encoding PRO830 in lung tumors. Hence this rejection based on the above references is moot.

The Examiner further says that "(i)t does not necessarily follow that a decrease in copy number of the mRNA results in a change in protein expression that would correlate to the disease state." The Examiner cites Haynes *et al.* to show that "protein levels couldn't be accurately predicted from the level of the corresponding mRNA transcript." The Examiner adds "(g)iven how small the DNA copy number of PRO830 increased, and the evidence provided by Haynes *et al.*, Pennica *et al.*, and Konopka *et al.*, it was clear that one skilled in the art would not assume

that a small increase in gene copy number would correlate with significantly increase mRNA of protein levels."

Applicants submit that, the teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. For instance, Pennica *et al.* studies only the WISP family of genes and Konopka *et al.* bases its conclusion solely upon the analysis of the *abl* gene. Thus, Applicants submit that these references do not conclusively establish a *prima facie* case for lack of utility. Further, as discussed previously in their response of August 19, 2004, Applicants submit that the teachings of Haynes *et al.* in fact meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Hayes shows that there was a *general* positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins even though the correlation is "not strictly linear" thereby not enabling one to accurately predict protein levels from mRNA levels. In fact, a careful look at Figure 1 of Haynes indicates that few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, Applicants maintain that contrary to the Examiner's position, the Haynes data actually supports the Polakis' statement that, in general, a positive correlation exists between mRNA and protein levels (even though the correlation may not be linear which prevents the data from being useful for accurately predicting protein levels from mRNA levels) and that the Examiner's rejection is based on a misrepresentation of the scientific data presented by Haynes *et al.*

Further and in contrast, Applicants had submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Applicants' Response filed August 19, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declaration of Dr. Paul Polakis (made of record in Applicants' Response filed August 19, 2004), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels . Applicants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their

GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (*i.e.,* that it is more likely than not informative of the protein level).

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* the Polakis Declaration and the widespread use of array chips, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Detecting the presence or absence of PRO830 polypeptides would be useful in the diagnosis of lung cancer and such a utility would be evident to one skilled in the art based on the data presented in the specification. Therefore, one of skill in the art would reasonably expect in this instance, that the PRO830 polypeptide is concomitantly overexpressed. Thus, the claimed PRO830 polypeptides also have utility in the diagnosis of lung cancer.

The Examiner further does not accept the teachings of the Polakis nor the Ashkenazi Declaration and maintains that it does not necessarily follow that a decrease in copy number of the mRNA results in a change in protein expression that would correlate to the disease state.

Applicants further respectfully draw the Examiner's attention to the Utility Examination Guidelines, Part IIB, 66 Fed. Reg. 1098 (2001) which states that, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statements in question from Dr. Polakis, an expert in the field, should be viewed in the context his statements regarding his personal research on human genes for which he isolated mRNA and studied the mRNA-protein correlations. For example, Dr. Polakis says:

> "In the course of the research conducted by Genentech's Tumor Antigen Project, we have employed a variety of scientific techniques for detecting and studying differential gene expression in human tumor cells relative to normal cells, at genomic DNA, mRNA and protein levels. An important example of one such technique is the well known and widely used technique of microarray analysis which has proven to be extremely useful for the identification of mRNA molecules that are differentially expressed in one tissue or cell type relative to another. In the course of our research using microarray analysis, **we have**

> **identified approximately 200 gene transcripts** that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, **we have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells.** We have then compared the levels of mRNA and protein in both the tumor and normal cells analyzed" (emphasis added).

Further, as Dr. Polakis himself clearly acknowledges, exceptions to the central dogma exist, and he qualifies this statement in his declaration by saying:

> "While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Applicants submit that Dr. Polakis' statements would be considered reasonable and accurate by one skilled in the art, as required by the Utility guidelines, hence the Examiner's request for further evidentiary support is improper.

Regarding the Examiner's rejection based on Hu, Applicants maintain that this reference does not support the Examiner's conclusions that "gene amplification does not necessarily result in increased protein levels." For instance, the Hu *et al.* reference bases its conclusions on ***statistical analysis*** *of information from published literature* which is evidenced by its title: "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining" and by its statement: "We have utilized a computational approach to *literature mining* to produce a comprehensive set of gene-disease relationships (emphasis added)." Further, Hu *et al.* state that they "compared the MedGene *breast cancer gene list* to a gene expression data set generated from *micro-array* analysis comparing *breast cancer and normal breast tissue samples*." (emphasis added; see page 408, right column). Therefore, Applicants submit that Hu's results were based on "statistical data," in which, by their own admittance, data had to be manipulated to "manage" the resulting outcome. For example, the authors admit, at least on page 406, right column, that "[i]nitial attempts at search the literature....revealed several sources of false positive and false negatives" which were "difficult to manage." Thus, to minimize such false positives, certain genes "had to be eliminated entirely, thereby reducing the false positive rate *but unavoidably underrepresenting some genes*" (emphasis added). Applicants submit that Hu's

conclusions are based on statistical data rather than experimental (gene amplification) data presented in the instant application. While Hu's data could be useful for understanding gene relationships for a class of genes, for example, breast cancer genes, the Hu reference does not demonstrate that "gene amplification does not necessarily result in increased protein levels in general" because: (1) it only studies gene relationships in breast cancer genes, and (2) because the results are generated through statistical analysis which was managed to "underpresent some genes." Therefore, the Examiner had not established that **it is more likely than not** that gene amplification does not necessarily result in increased protein levels in general by citing a reference that only discusses "breast cancer genes" while "underrepresenting some genes" and relies on "statistical data" for the same. Applicants further note that Hu *et al.* studied the relationship between mRNA and protein data.

Regarding the rejection based on the Wang *et al.* reference to show that, "further action should be taken to characterize the functions of a particular gene of interest, including....validation for the importance of the gene in disease processes," Applicants submit they have already asserted in their response of August 19, 2004 that utility for PRO830 is based on the gene amplification data. That is, they performed the necessary experiments (gene amplification data) to establish utility for PRO830 and have asserted its role as a protein marker to diagnose lung cancer. Therefore, Applicants submit that the Hu and Wang references cited by the Examiner do not provide evidence for lack of utility.

Regarding the Examiner's comment regarding the Ashkenazi declaration on page 10 of the instant Office action that "(n)o evidence is provided of a tumor where this difference has aided classification, and there is further no evidence of a tumor wherein a difference in expression relative to amplification aided a clinician in ruling out potential treatment agents."

Applicants respectfully submit that even if there is no correlation between gene amplification and increased mRNA/protein expression, (which Applicants expressly do not concede), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Applicants submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Applicants' Response filed August 19, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. Hanna and Mornin taught that the HER-2/neu gene was shown to be

amplified in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Even when the protein was not over-expressed, the information could lead to a more accurate classification of the cancer and a more effective treatment of it. This lead to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu. Accordingly, Applicants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed PRO830 polypeptides.

Therefore, Applicants submit that, for the reasons discussed above, based on the cited references Pennica, Konopka, Haynes and Wang, the Examiner has not made a *prime facie* case for lack of utility since these references have not met the "more likely than not" standard. Therefore, barring evidence to the contrary, utility for PRO830 has been established. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. §101 and §112, first paragraph, be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney Docket **No. 39780-2730P1C10**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 13, 2005

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